Statistical Review and Evaluation

Date: February 18, 1999

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Applicant: Serono Laboratories, Inc.

Name of Product: Interferon-β1a (Rebif^{R})

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SYNOPSIS OF APPLICATION

This application, submitted on February 27, 1998, is for approval of Rebif, an interferon-β1a manufactured by Ares Serono, for the treatment of patients with relapsing-remitting and XXXXXXXXXX MS. The proposed package insert states the following:

> "Rebif® (interferon-beta-1a) is indicated for the treatment of patients with relapsing-remitting multiple sclerosis XXXXXXXXXX. Rebif® decreases the frequency XXXXXXXXXX of clinical exacerbations and delays XXXXXXXXXX accumulation of physical disability. XXXXXXXXXX efficacy in patients with progressive multiple sclerosis have not been established.."

Two dose regimens are being proposed: IFN-β1a at 22 mcg subcutaneously three times a week and 44 mcg subcutaneously three times a week.

Summary (efficacy)

- Rebif caused statistically significant decreases in exacerbation counts that were robust to sensitivity and subgroup analyses. Time to exacerbation was also affected, but duration of exacerbations was not changed by treatment with Rebif. Differences in counts of moderate and severe exacerbations paralleled those in counts overall. Differences between treatments in exacerbation parameters trended toward a dose relation, with no statistically significant differences between active treatments.
- Other clinical outcomes as defined in the protocol (steroid use in MS, hospitalization rates for MS) were supportive of efficacy.
- Rebif caused statistically significant increases in the important supportive endpoint, time to disability. This effect was robust to sensitivity and subgroup analyses.
- Rebif caused decreases in MRI measures of MS disease pathology and activity. The differences between treatments in PD/T2 lesion areas were statistically significant, in distinction to changes seen in clinical parameters. However, differences between treatments in activity measures as determined in subgroups were not statistically different.
- While the analysis of considerably more subjects than projected by sample size estimates(560 as opposed to around 300) could have the effect of increasing the statistical power for a specific alternative, it would not change the magnitude of the clinical effect and the overall conclusions of the trial.
- Post-hoc analysis of EDSS ≥4 group showed dose-related treatment trends.

PRODUCT INFORMATION

Rebif is a syringe pre-filled with a liquid formulation of IFN-β1a. The interferon in Rebif is a glycoprotein produced in recombinant mammalian (Chinese Hamster Ovary or CHO) cells, with an amino acid sequence identical to that of fibroblast-derived human interferon-β. Rebif is formulated as a solution with human albumin, mannitol, sodium acetate, and water for injection.

SUMMARY OF CLINICAL TRIALS OF REBIF IN MS

Serono has completed 2 clinical trials in MS: XXXXXXXXXX, a 72-subject, open-label trial of subjects with RRMS, and XXXXXXXXXX, a 560-subject, placebo-controlled trial of subjects with RRMS that is the focus of this review. The primary endpoint of XXXXXXXXXX was MRI evidence of brain lesions; the primary endpoint of XXXXXXXXXX was exacerbations of MS. Trial XXXXXXXXXX was completed after XXXXXXXXXX was initiated.

XXXXXXXXXX

DOSE SELECTION FOR PLACEBO-CONTROLLED TRIAL

Dose selection for the placebo-controlled trial XXXXXXXXXX was based upon Serono's assessment of tolerability of the 22 mcg and 44 mcg doses of their IFN-β1a in non-MS indications, as well as their assessment of Rebif's expected ratio of benefit to adverse effects in comparisons with Avonex and Betaseron.

SCOPE OF REVIEW

The focus of this review will be on XXXXXXXXXX, as this constitutes the bulk of evidence for the efficacy and safety of Rebif in RRMS. Results from the 72-subject open-label trial XXXXXXXXXX will be summarized, but both its open-label design and the small number of subjects investigated make its contribution to the understanding of Rebif weak. Therefore, an integrated summary of efficacy will not be presented. Results from the integrated summary of safety, including adverse event reports in unblinded MS trials, will be presented. The 120-day safety update is reviewed, as well as post-marketing data presented in the submission.

Serono has submitted information regarding the orphan drug status of the beta-interferons, and proposed that Rebif should not be blocked from approval at this time by the orphan drug regulations. These issues are not included within the scope of this review document. Reviews discussing these issues have been written by Dr. M. Walton, dated October 1998 and February 1999. These reviews should be examined for all information and assessments with regard to orphan drug issues.

TRIAL XXXXXXXXXX

DESIGN

CBER commented upon a preliminary version of the protocol for this trial in December, 1993. The final version was not received for comment until after the analysis was completed.

Title: A multicentre, randomized, double-blind, placebo-controlled, phase III study of subcutaneous Rebif™ (recombinant human interferon-beta) in the treatment of relapsing-remitting multiple sclerosis

Code: XXXXXXXXXX

Study dates: May 1994 to March 1997

Objectives

The stated primary objective of the trial was to investigate the effects of Rebif at two doses, 6 MIU and 12 MIU, compared to placebo, on the number of exacerbations.

The stated secondary objectives of the trial were to determine the effects of Rebif at the two doses stated above, compared to placebo, on

- duration and severity of exacerbations, time to first exacerbation, and proportion of patients remaining exacerbation-free at 1 and 2 years
- disease activity as measured by numbers of active lesions on monthly cranial T_2-weighted and T_1-weighted Gd-MRI
- burden of disease as measured by cranial T_2-weighted MRI
- deterioration of disability
- safety and tolerability
- need for steroid therapy and hospitalization for MS

Design

This was a double-blinded trial of two dose levels of active agent as compared to placebo, conducted at 22 sites in Canada, and the European Union. Randomization was stratified by center in blocks of 6. Imaging was performed at various sites but analyzed at one site (XXXXXXXXXX). Imaging was performed biannually for all subjects, with two subgroups selected to receive more frequent MRIs. An independent panel performed ongoing review of safety information and supervision of the interim analysis.

Treatment

Trial treatment was to be placebo or Rebif at either 22 mcg or 44 mcg TIW, subcutaneously, for 2 years. It was distributed as 42 vials (a little more than a 3-month supply) containing 0.65 ml of Rebif or placebo solution (the maximal amount to be withdrawn was 0.5 ml). (It should be noted that the formulation for marketing is the same, but is distributed in prefilled syringes.) Placebo was the same solution as active treatment, without interferon; it consisted of sodium acetate, 0.01 M, with mannitol and human serum albumin. Treatments were to be injected by the subject or a family member at the same time each day, preferably in the evening.

To ameliorate the unblinding effects of sudden administration of full dose of interferon, subjects were to titrate their dose in the initial 8 weeks of the trial. For the first 2-4 weeks of treatment, 1/5 of the volume of trial agent was to be administered; then ½ of the volume for the second 2-4 weeks, followed by the full dose. This schedule was a rough guideline that could be modified individually. Subjects were to be excluded if they could not tolerate doses higher than 1/5 dose by the beginning of the 5^{th} week, or withdrawn if unable to tolerate a full dose by the end of 8 weeks.

Dosing could be adjusted to ½ dose in the event of a persistent WHO grade 2 toxicity; the occurrence of a causally related grade 3 toxicity would allow the reduction or interruption of the dose, with return to full dose or discontinuation related to level of persistent toxicity. Subjects were to be withdrawn from treatment in the event of a grade 4 toxicity due to Rebif. However, there were to be no interruptions or withdrawals for neurological events.

Paracetamol (acetaminophen) was to be given at the discretion of the investigator prophylactically and to ameliorate constitutional symptoms at a dose of 325-1000 mg as required during the treatment period.

Primary endpoint

The primary endpoint was the number of protocol-defined exacerbations per subject, using the following definition:

> "..the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by appropriate new neurological abnormality, or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and preceded by stability or improvement for at least 30 days."

Secondary endpoints

Secondary endpoints fell into 3 general categories: exacerbation-related, disability-related, and related to imaging of lesions on MRI. They were not ranked in order of importance by Serono. They were stated as follows:

- disease activity as measured by the number of active lesions on MRI (new, enlarging, recurrent on PD/T2 or enhancing on a T1-Gd scan)
- duration of exacerbations
- severity of exacerbations as defined by changes in the Scripps NRS scale
- time to 1st exacerbation
- proportion of subjects remaining exacerbation-free at 1 and 2 years
- burden of disease as defined by the total area of all lesions on MRI
- deterioration of disability as measured by change in EDSS
- need for steroid therapy and hospitalization for MS

Safety endpoints

Listed safety endpoints included lab tests, vital signs, and psychological status assessed by psychometric testing.

Interim analysis

One interim analysis was planned. It was to occur when 100 subjects/arm had completed 1 year on study. Its purpose was to re-randomize placebo subjects to the treatment groups if efficacy were found in the high-dose group at p=.005.

Serono stated that for analysis of monthly MRI results, the interim analysis would include all the data; thus no adjustment would be considered necessary and the analysis would be final.

Individuals allowed to see the results of the interim analysis were to be the vice president for Medical Affairs, the Therapeutic Director, a responsible biometrician from Serono, and persons not otherwise involved with the trial including an external neurologist, neuroradiologist, biometrician, and a clinical expert in the use of IFN-β.

Final analysis

The original protocol specified the primary analytical population as all subjects reaching the full dose (0.5 ml) of the trial agent by week 8; this was changed in amendment 1 to be an intent-to-treat population defined as all subjects randomized. There was to be no imputation for missing data.

The analytical method for the primary endpoint was to be a Cochran-Mantel-Haenszel ANOVA stratified by center, using observed counts of exacerbation as the scores. All 3 treatments were to be compared simultaneously and pairwise.

The protocol did not specify analytical methods for each secondary endpoint. Rather, a summary statement was made:

> "Categorical variables such as proportions of exacerbation-free subjects or the severity of exacerbation will be analyzed by Cochran-Mantel-Haenszel chi-square test, stratified by center. Analysis of variance (ANOVA) taking the center effect into account will be applied for continuous variables. The time to first exacerbation was to be analyzed with the log-rank test, stratified by center. The burden of disease will be measured in terms of percent change because of the variability of the different MRI machines used in the various centers. The changes in EDSS as well as the ambulation index and arm index, will also be analyzed and compared between the treatment groups."

Trial enrollment

Five hundred and sixty subjects were randomized and treated; 187 in the placebo group, 189 in the IFN 22 mcg SC TIW group, and 184 in the IFN 44 mcg SC TIW group. The first day of treatment for the first subject was May 11, 1994; for the last, March 2, 1995. Among the 22 sites, 8 enrolled exactly 20 subjects and 6 enrolled exactly 30 subjects. There was not a preponderance of subjects at any one site, with 40 the highest number enrolled at one site (another site enrolled 39). One site each enrolled 19, 21, 22, 24, 27, and 28 subjects. In addition, subjects were evenly distributed by treatment assignment, with a maximal enrollment disparity among the treatment arms of 2 at only 3 sites.

ANALYSIS AND RESULTS:

Baseline characteristics of subjects were well balanced among the treatment arms. Race distribution was characteristic of the MS population. The ratio of males to females more closely approximated the overall population ratio (1:2) in the two treatment groups than in the placebo group, where the ratio of males was lower (1:3). There was a slightly lower time since the onset of disease in the placebo group, but indices of disease activity and extent were similar.

The percentages of subjects followed to the completion of the trial at 24 months was 95.2% overall: the highest number of subjects followed to the completion of the trial was in the high-dose group (94.7% placebo, 93.7% in the low-dose group, and 97.3% in the high-dose group).

Table 1 shows the time spent on the study by treatment group.

Table 1. Time on study (days)

	Placebo *n=187*	IFN 22 mcg TIW *n=189*	IFN 44 mcg TIW *n=184*
mean +/- sem	711 +/- 7.3	707 +/- 8.3	723 +/- 5.0
median (Q1, Q2)	730 (729,736)	730 (729, 736)	731 (729,736)

EFFICACY – PRIMARY ENDPOINT: Number of Exacerbations per Subject

Serono attributed 0 exacerbations to those subjects who were lost to follow-up without an exacerbation, such subjects were found only in the placebo and low-dose groups. This manipulation was performed for 2 and 6 subjects respectively at 2 years (1.1 and 3.2% of subjects at 2 years). This resulted in a conservative assignment for comparing high dose to placebo, but not for comparing low dose to placebo.

Statistical comparisons were performed using a log linear model taking into account center and time on study. The numbers of subjects with a <95% of time on study in placebo, low, and high-dose groups were 11, 12, and 5, respectively. These results are given below in Table 2. This table shows Serono's statistical analysis of the primary endpoint: mean numbers of exacerbations experienced by subjects in each treatment arm.

Table 2. Mean exacerbation count per subject at 1 and 2 years

time in study	placebo *n=187*	IFN 22 mcg TIW *n=189*	IFN 44 mcg TIW *n=184*	p-value IFN 22 vs. placebo	p-value IFN 44 vs. placebo	p-value IFN 22 vs. IFN 44
1 year	1.5	1.0	0.9	<0.0001	<0.0001	0.34
2 years	2.56	1.82	1.73	0.0002	<0.0001	0.37

CBER confirmed these analyses. CBER also performed unadjusted (for center and time in study) analyses and also sensitivity analyses assigning different exacerbation scores to those subjects who were lost to follow-up without an exacerbation. Serono's analysis of the numbers of exacerbations attributed 0 exacerbations to 5 subjects at 1 year (1 placebo, 4 low-dose) and 8 subjects at 2 years (2 placebo, 6 low-dose) with missing observations. CBER determined p-values (unadjusted for time on study), using a log-link procedure, deleting the missing values and attributing the median (median = 1.0 at the end of one year and 2.0 at the end of two years) and worst values (worst = 5.0 at the end of one year and 10.0 at the end of two years) overall to the missing ones. As can be seen from the following Table 3, none of the analyses changed the conclusions regarding the primary endpoint as presented in Table 2.

Table 3. P-values for the primary endpoint, mean numbers of exacerbations (unadjusted for center or time on study), using different imputation methods

Imputation Method	Time on Study = 1 year			Time on Study = 2 years		
	High Dose vs. Placebo	Low Dose vs. Placebo	High vs. Low Dose	High Dose vs. Placebo	Low Dose vs. Placebo	High vs. Low Dose
Serono's	< 0.0001	< 0.0001	0.3268	< 0.0001	0.0002	0.3913
deletion	< 0.0001	0.0001	0.2276	< 0.0001	0.0005	0.2092
median	< 0.0001	0.0001	0.2082	< 0.0001	0.0005	0.1687
worst	< 0.0001	0.0005	0.1195	< 0.0001	0.0027	0.0772

Subgroup Analyses:

Various subgroup analyses for the mean exacerbation counts by treatment group, center, age group, sex, baseline EDSS scores etc. baseline burden of disease (BOD) were done. The effect of treatment was consistent across various centers, age groups, baseline EDSS scores, sex, BOD etc. The results are given in Appendix C.

Secondary Endpoints:

Duration of Exacerbations:

The duration of exacerbations was similar for either treatment with a mean of 47-48 days for all groups.

Exacerbation Severity:

There were more subjects with least number of moderate to severe exacerbations in the active treatment groups.

Secondary endpoint: Time to 1st (and 2nd) exacerbation

Table 4 shows the time to 1st and 2nd exacerbation as presented by Serono. The time to 2nd exacerbation was not prospectively defined as an endpoint.

Table 4. Median time to 1st and 2nd exacerbation (days)

	Placebo *n=187*	IFN 22 mcg TIW *n=189*	IFN 44 mcg TIW *n=184*	p-value IFN 22 vs. placebo	p-value IFN 44 vs. placebo	p-value IFN 22 Vs IFN 44
1st exacerbation	135	229	288	0.0008	<0.0001	0.16
2nd exacerbation	449	702	Not reached	0.002	<0.0001	0.12

Note: the statistical test was a Cox proportional hazards model taking center into account

Secondary endpoint: Proportion of subjects exacerbation-free

Table 5 shows the proportion of subjects exacerbation-free, as presented by Serono. Subjects who were lost to follow-up without an exacerbation were censored from the analysis.

Table 5. Exacerbation-free subjects (% of group)

time in study	placebo	IFN 22 mcg TIW	IFN 44 mcg TIW	p-value IFN 22 vs. placebo	p-value IFN 44 vs. placebo	p-value IFN 22 vs. IFN 44
	% *(n)*	% *(n)*	% *(n)*			
1 year	22 *(186)*	37 *(185)*	45 *(184)*	0.0009	<0.0001	0.11
2 years	15 *(185)*	25 *(183)*	32 *(184)*	0.014	<0.0001	0.08

Note: the statistical test was a logistic regression taking center into account.

The effects of IFN were consistent across most of the exacerbation-related secondary endpoints: presence or absence of exacerbation and time to exacerbations and their severity. One endpoint, duration, was not affected by IFN treatment. The effect of IFN treatment on the incidence of exacerbations of each severity paralleled that for overall exacerbations. Thus it is not clear that there was an independent effect on severity of exacerbations.

Secondary endpoint: Deterioration in disability (time to confirmed disability and percent progressors)

Figure 1 shows the Kaplan-Meier analysis of the time to first 3-month confirmed progression in EDSS disability, censoring those lost to follow-up without a progression.

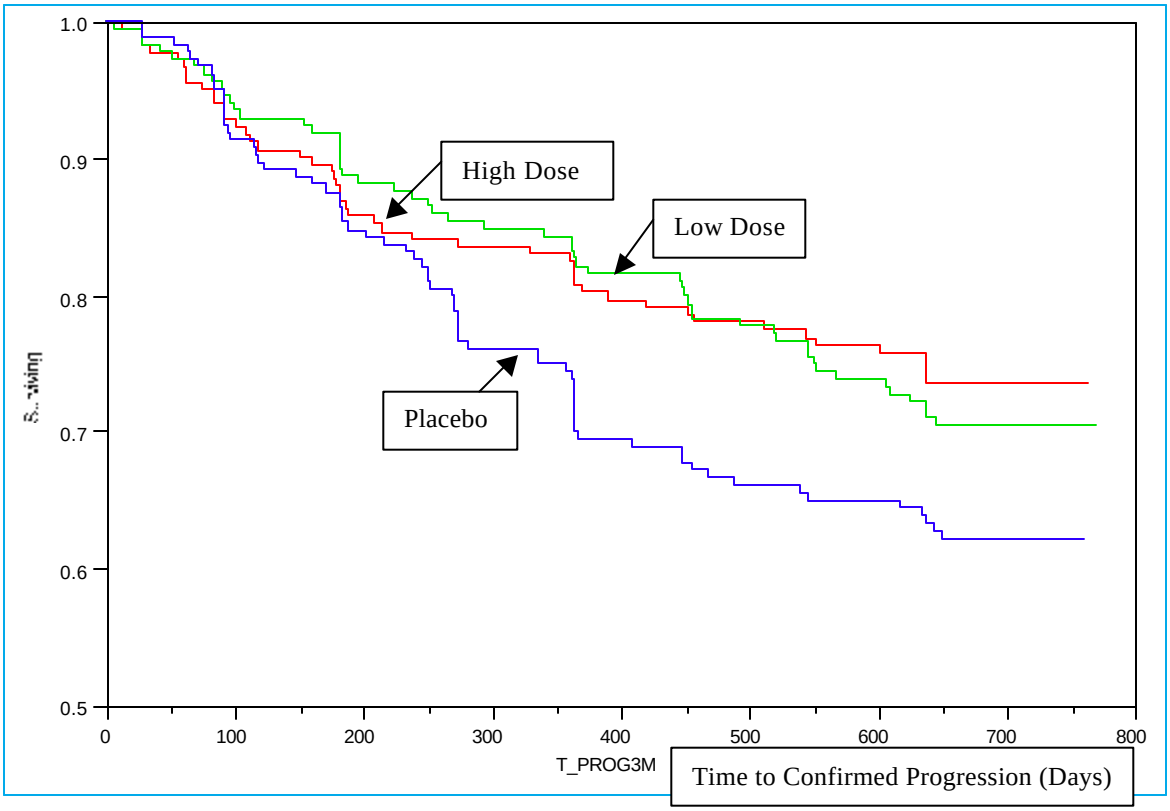
Figure 1: Percents of subjects with 3-month confirmed EDSS deterioration

Percent without 3-month confirmed disability deterioration ("surviving")

Product-Limit Survival Estimates

Time Variable: T_PROG3M (Time to Confirmed Progression in Disability)

Censoring Variable: CENSOR (if no progression) -- Survival Plot



Tests Between Groups (Comparing all three treatment groups)

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	5.9728	2	0.0505
Wilcoxon	5.6911	2	0.0581

Tests Between Groups (Comparing High Dose to Placebo)

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	4.9595	1	0.0259
Wilcoxon	4.3613	1	0.0368

Tests Between Groups (Comparing Low Dose to Placebo)

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	3.3388	1	0.0677
Wilcoxon	3.6580	1	0.0558

Tests Between Groups (Comparing Low Dose to High Dose)

Test	Chi-Square	DF	Prob>ChiSq
Log-Rank	0.2372	1	0.6282
Wilcoxon	0.1087	1	0.7417

These results are confirmatory of the effects of IFN on increasing the time to progression in disability. As Serono concluded, there was no statistically significant difference between the two doses on prolongation of time to 3-month EDSS confirmed disability. The percent of group with 3-month confirmed deterioration at 2 years was 37.7, 29.4 and 26.4 for placebo, low dose and high dose respectively.

End-of-trial confirmed deterioration in disability status

The time to confirmed progression in disability analysis measures the first time that a confirmed deterioration occurs in a subject's status. However, in some cases status may improve. Subjects may end the trial unchanged or even better than when they started. CBER determined the percentages of subjects who ended the trial with a 3-month confirmed deterioration in disability. Two analyses were performed (Table 13):

- analysis 1: subjects with both month 21 and month 24 EDSS values
- analysis 2: similar to analysis 1, with addition of subjects a) whose last values were before the end of the trial, where the last value represented a deterioration and the previous value also represented a deterioration (these values may have been more than 3 months apart) and b) those with a month 24 value, but whose previous value was more than 3 months prior.

Analysis of the confirmed Progression:

Analysis 1: Patients whose EDSS evaluations were available on the last two visits (24 months & 21 months)

Confirmed progression was defined as 'Yes' if the difference in the EDSS value at 21 months and baseline EDSS value was greater than 1 if the baseline EDSS was smaller than 6.0 or the difference was greater than or equal to 0.5 if the baseline EDSS was larger than or equal to 6.0. Otherwise, the confirmed progression was defined as 'No'. There were 529 patients out of a possible 560 patients who had EDSS values both at 21 months and 24 months.

TABLE OF CONFIRMED PROGRESSION BY TREATMENT
For Patients who had both 21 months and 24 months
EDSS values available

CONFIRMED Frequency, Col Pct	TREAT(Treatment Group) Rebif 44 mcg	Rebif 22 mcg	Placebo	Total
NO	162	155	151	468
	91.01	89.08	85.31	
YES	16	19	26	61
	8.99	10.92	14.69	
Total	178	174	177	529

Two sided exact p-value:

Comparing all three groups (i.e. all three dose groups have similar response) p = 0.1006
Comparing Rebif 44 mcg to placebo: p = 0.1030
Comparing Rebif 22 mcg to placebo: p = 0.3391

Conclusion: The treatment does not offer any significant advantage in reducing the percent of confirmed progressors. However, there is a trend favoring treatment, especially high dose.

Analysis 2: All Patients – Including Those Whose Outcome Could be Determined:

There were a total of patients who either stopped the treatment early (24) or did not have EDSS evaluations available on both 21 and 24 months (6). CBER determined the progression outcome of 23 patients based on the specified criteria. The outcome of the remaining 7 patients could not be determined based on the algorithm, i.e., they do not have enough time for evaluation. The results are given below:

TABLE OF CONFIRMED PROGRESSION BY TREATMENT
For All Patients Whose Outcome could be determined

CONFIRMED Frequency, Col Pct	TREAT(Treatment Group) Rebif 44, mcg	Rebif 22, mcg	Placebo	Total
NO	167	164	156	487
	91.3	88.2	84.8	
YES	16	22	28	66
	8.7	11.8	15.2	
Total	183	186	184	553

Two sided exact p-value:

Comparing all three groups (i.e. all three dose groups have similar response) p = 0.0591

Comparing Rebif 44 mcg to placebo: p = 0.0762

Comparing Rebif 22 mcg to placebo: p = 0.3646

Conclusion: The treatment does not offer any significant advantage in reducing the percent of confirmed progressors. However, there is a trend favoring treatment, especially high dose.

Active treatment tended to reduce the numbers of subjects with confirmed deterioration in disability at the end of the trial, with a trend toward a dose effect.

The Missing Data for the EDSS Values at Base line and months are given in Appendix A.

CBER exploratory analyses for differential efficacy – Subgroup Analyses

CBER examined exacerbation counts, deterioration in disability, and change in MRI lesion area in the subgroups of gender and baseline age, weight, EDSS, and MRI lesion area in an effort to ascertain if there is compelling evidence of a lack of benefit in any of these important categories of subjects. The results are given in Appendix B. Subjects with missing data were omitted.

These exploratory analyses failed to suggest critical thresholds of age, gender, weight, baseline EDSS, or baseline MRI PD/T2 lesion area outside of which the administration of IFN would reliably be expected not to confer benefit.

These post-hoc analyses suggest that efficacy was maintained for most parameters listed; the dose trend seen in the overall subject pool was maintained, as well.

Logistic Regression Analysis

Logistic Regression provides a method for constructing statistical models with multiple explanatory variables.

The predictive value of a variable, such as baseline EDSS, can be assessed by the percent contribution this variable makes to the reduction of the error sum of squares. In other words, the percent of variation explained by this variable in the multiple regression model should be computed.

Step-wise selection in PROC LOGISTIC procedure allows all variables to be treated individually. A cut-off significance is used to test if any variable is significant enough to enter the model (p=0.10, for example). Assuming there is at least one significant covariate, the most significant covariate starts the model building process. Next, the residuals between the model and the remaining variable are tested to evaluate significance and the most significant is added to the model. A more restrictive cut-off for significance is used to test if any variable is significant to stay in the model (e.g., p=0.05). When the last variable entered does not satisfy the stay criteria, it is removed and the preceding model is the final one.

It was desired to find out the significant predictors of the exacerbation rate at the end of one year and at the end of two years. Since the exacerbation free (Yes or No) at the end of one or two years is a dichotomous response variable, Logistic Regression Analysis is an appropriate way to analyze such data. Logistic regression analysis is often used to investigate the relationship between the response probability and the explanatory variables. Variable selection is a typical exploratory exercise in multiple regression when the interest lies in identifying important prognostic factors from a large number of explanatory variables.

The SAS LOGISTIC procedure fits linear logistic regression models for binary or ordinal response data by the method of maximum likelihood. Subsets of explanatory variables can be chosen by various model-selection methods.

Stepwise procedures for selection or deletion of variables from a model are based on a statistical algorithm which checks for the "importance" of variables, and either includes or excludes them on the basis of a fixed decision rule. The "importance" of a variable is defined in terms of a measure of the statistical significance of the coefficient for the variable. The most important variable, in statistical terms, is the one that produces the greatest change in the log-likelihood relative to a model not containing the variable. The entry criterion for a variable to enter the model was set at alpha = 0.10, and the stay criterion for a variable to remain in the model was set at alpha = 0.06. **Note that all the variable selection procedures are exploratory and can not be used as a basis for approval.**

Conclusions regarding Logistic Regression Analysis:

Exacerbation at the end of one year and two years:

Logistic regression analysis is modeling the probability that the patients had exacerbation at the end of one year and two years.

Overall Assessment (All three dose group – high dose, low dose and placebo) in the model:

The treatment and the baseline EDSS are significant predictor of the exacerbation at the end of one year. Patients with higher baseline EDSS levels and higher dose benefit significantly with reduced exacerbation rate as compared to lower EDSS and lower dose. Other variables such as Burden of disease, age and sex do not enter the model at significance level of 0.06.

The results are similar at the end of two years.

Comparing High Dose to Placebo at one year and two years:

The treatment and the baseline EDSS are significant predictor of the exacerbation at the end of one year. Patients with higher baseline EDSS levels and high dose benefit significantly with reduced exacerbation rate as compared to lower EDSS levels and placebo. Other variables such as Burden of disease, age and sex do not enter the model at significance level of 0.06.

The results are similar at the end of two years except that Baseline EDSS only marginally enters the model (p=0.0544).

Comparing Low Dose to Placebo at one year and two years:

The treatment, baseline EDSS and age are significant predictor of the exacerbation at the end of one year. Younger patients with higher baseline EDSS levels and low dose benefit significantly with reduced exacerbation rate as compared to older patients with lower EDSS levels and placebo. Other variables such as Burden of disease and sex do not enter the model at significance level of 0.06.

The results are similar at the end of two years except that Age only marginally enters the model (p=0.0562).

The results are given in Appendix D.

FURTHER ANALYSES – Sub-groups:

Further Analysis was done to explore the results of Logistic Regression Analysis. The histograms given in Appendix B show that patients with higher EDSS scores had greater benefit for both the dosage (6 MIU and 12 MIU) as compared to placebo. There is a suggestive trend in the age category group, which is not significant by logistic regression analysis after taking out effect due to treatment.

The bars in these histograms represent the percent of people who had at least one exacerbation in that category. The N's are given at the bottom.

The results are given in Appendix C and D.

Summary (efficacy)

- Rebif caused statistically significant decreases in exacerbation counts that were robust to sensitivity and subgroup analyses. Time to exacerbation was also affected, but duration of exacerbations was not changed by treatment with Rebif. Differences in counts of moderate and severe exacerbations paralleled those in counts overall. Differences between treatments in exacerbation parameters trended toward a dose relation, with no statistically significant differences between active treatments.
- Other clinical outcomes as defined in the protocol (steroid use in MS, hospitalization rates for MS) were supportive of efficacy.
- Rebif caused statistically significant increases in the important supportive endpoint, time to disability. This effect was robust to sensitivity and subgroup analyses.
- Rebif caused decreases in MRI measures of MS disease pathology and activity. The differences between treatments in PD/T2 lesion areas were statistically significant, in distinction to changes seen in clinical parameters. However, differences between treatments in activity measures as determined in subgroups were not statistically different.
- While the analysis of considerably more subjects than projected by sample size estimates(560 as opposed to around 300) could have the effect of increasing the statistical power for a specific alternative, it would not change the magnitude of the clinical effect and the overall conclusions of the trial.
- Post-hoc analysis of EDSS ≥4 group showed dose-related treatment trends.

Appendix A
The Missing Data
EDSS Values at Base line and months

	Treatment	Patient #	Base	3	6	9	12	15	18	21	24	99	
1	Rebif 44 mcg	XXXXXXXXXX	2.5	.	.	.	.	.	.	.	.	.ND	
2	Rebif 44 mcg	XXXXXXXXXX	6.0	6.0	6.0	6.0	6.0	6.0	6.0	.	.	. N	
3	Rebif 44 mcg	XXXXXXXXXX	1.5	2.5	1.5	2.0	3.5	2.5	.	.	.	. N	
4	Rebif 44 mcg	XXXXXXXXXX	3.0	4.0	3.0	.	.	.	.	.	.	. N	
5	Rebif 44 mcg	XXXXXXXXXX	1.5	1.0	3.0	1.5	2.5	2.0	2.0	3.0	.	. N	
6	Rebif 44 mcg	XXXXXXXXXX	1.5	1.5	1.0	1.5	0.0	1.5	1.5	.	1.0	. N	
7	Rebif 22 mcg	XXXXXXXXXX	1.0	2.5	5.0	2.0	.	.	.	.	.	2.0 Y	
8	Rebif 22 mcg	XXXXXXXXXX	1.0	2.5	2.5	2.0	0.0	.	.	.	.	. N	
9	Rebif 22 mcg	XXXXXXXXXX	2.5	.	3.0	3.0	2.5	4.0	4.0	.	.	. N	
10	Rebif 22 mcg	XXXXXXXXXX	2.5	2.5	2.5	2.5	8.0	.	.	.	.	. N	
11	Rebif 22 mcg	XXXXXXXXXX	3.5	3.5	3.5	.	.	.	.	.	.	. N	
12	Rebif 22 mcg	XXXXXXXXXX	1.0	.	0.0	.	1.0	.	.	.	.	. N	
13	Rebif 22 mcg	XXXXXXXXXX	1.5	.	.	.	.	.	.	.	.	2.5ND	
14	Rebif 22 mcg	XXXXXXXXXX	3.5	2.5	2.5	3.5	.	3.5	5.5	.	4.0	. N	
15	Rebif 22 mcg	XXXXXXXXXX	2.0	2.0	2.0	2.0	2.0	2.0	2.0	.	2.0	. N	
16	Rebif 22 mcg	XXXXXXXXXX	1.0	1.0	1.5	1.0	.	.	.	.	.	. N	
17	Rebif 22 mcg	XXXXXXXXXX	2.0	.	.	.	.	.	.	.	.	.ND	
18	Rebif 22 mcg	XXXXXXXXXX	3.5	3.5	4.0	4.5	4.0	4.5	6.5	5.5	.	. Y	
19	Rebif 22 mcg	XXXXXXXXXX	2.5	3.0	3.5	3.5	3.5	3.5	4.0	.	.	. Y	
20	Rebif 22 mcg	XXXXXXXXXX	4.0	.	.	.	.	.	.	.	.	.ND	
21	Rebif 22 mcg	XXXXXXXXXX	1.0	1.5	1.5	1.0	1.0	2.0	1.5	.	1.5	. N	
22	Placebo	XXXXXXXXXX	3.5	6.0	6.5	6.0	6.0	.	.	.	.	8.0 Y	
23	Placebo	XXXXXXXXXX	2.5	1.0	2.0	1.5	2.0	.	.	.	.	. N	
24	Placebo	XXXXXXXXXX	2.0	.	.	.	.	.	.	.	.	.ND	
25	Placebo	XXXXXXXXXX	4.0	5.5	.	.	.	.	.	.	.	.ND	
26	Placebo	XXXXXXXXXX	3.0	3.5	5.0	6.5	6.0	6.5	6.5	.	.	. Y	
27	Placebo	XXXXXXXXXX	1.5	1.5	1.5	3.0	.	.	.	.	.	3.0 N	
28	Placebo	XXXXXXXXXX	0.0	0.0	2.0	2.5	0.0	.	.	.	.	0.0 N	
29	Placebo	XXXXXXXXXX	3.0	3.0	3.5	.	.	.	.	.	.	. N	
30	Placebo	XXXXXXXXXX	4.5	4.5	4.5	4.5	4.5	4.5	4.5	.	.	. N	
31	Placebo	XXXXXXXXXX	4.0	5.0	.	.	.	.	.	.	.	.ND	

The last column refers to the outcome related to confirmed progression as defined by the algorithm. Y means ‘yes’, the patient has confirmed progression, ‘N’ is ‘No’ and ND means the outcome could not be determined by using the algorithm as there is not enough time for evaluation.

APPENDIX B

Exacerbation Count at 1 Year vs. EDSS

BL	**Placebo**				**Low Dose**				**High Dose**			
EDSS	n	mean	sem	Medi-an	n	mean	sem	median	n	mean	sem	median
0 - 1.5	62	1.13	0.14	1.0	57	0.77	0.12	1.0	58	0.83	0.15	0.5
2 – 2.5	53	1.47	0.19	1.0	51	1.14	0.15	1.0	48	0.96	0.15	1.0
3 – 3.5	44	1.84	0.18	1.5	46	1.22	0.18	1.0	47	1.09	0.16	1.0
>=4	28	1.82	0.21	2.0	35	0.89	0.13	1.0	31	0.81	0.17	1.0
Overall	187	1.5	0.09	1.0	189	1.00	0.07	1.0	184	0.92	0.08	1.0

Exacerbation Count at 2 Years vs. EDSS

BL	**Placebo**				**Low Dose**				**High Dose**			
EDSS	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
0 - 1.5	62	1.97	0.23	1.0	57	1.3	0.17	1.0	58	1.62	0.27	1.0
2 – 2.5	53	2.53	0.29	2.0	51	2.08	0.25	2.0	48	2.0	0.25	2.0
3 – 3.5	44	3.09	0.32	2.5	46	2.17	0.31	1.5	47	1.94	0.26	2.0
>=4	28	3.07	0.35	3.0	35	1.83	0.25	2.0	31	1.23	0.22	1.0
Overall	187	2.6	0.15	2.0	189	1.82	0.13	2.0	184	1.73	0.13	1.0

Exacerbation Count at 1 Year vs. Sex

BL	**Placebo**				**Low Dose**				**High Dose**			
SEX	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
Male	46	1.63	0.20	1.0	63	0.98	0.14	1.0	62	0.95	0.13	1.0
Female	141	1.45	0.10	1.0	126	1.01	0.09	1.0	122	0.91	0.10	1.0

Exacerbation Count at 2 Years vs. Sex

BL	**Placebo**				**Low Dose**				**High Dose**			
Sex	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
Male	46	2.74	0.32	2.0	63	1.89	0.24	2.0	62	1.84	0.23	1.0
Female	141	2.50	0.17	2.0	126	1.79	0.14	1.5	122	1.68	0.16	1.0

Exacerbation Count at 1 Year vs. Base Weight

BL	**Placebo**				**Low Dose**				**High Dose**			
Weight	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< = 59	54	1.57	0.19	1.0	55	1.02	0.14	1.0	41	0.93	0.18	1.0
(59 – 67]	50	1.30	0.16	1.0	44	0.86	0.15	1.0	47	0.79	0.13	1.0
(67 – 77]	43	1.56	0.19	1.0	42	1.24	0.18	1.0	48	0.98	0.17	1.0
> 77	40	1.58	0.19	1.0	48	0.90	0.13	1.0	48	1.00	0.15	1.0

Exacerbation Count at 2 Years vs. Base Weight

BL	**Placebo**				**Low Dose**				**High Dose**			
Weight	n	mean	sem	median	n	mean	sem	median	n	mean	sem	Median
< = 59	54	2.59	0.32	2.0	55	1.84	0.22	1.0	41	1.78	0.32	1.0
(59 – 67]	50	2.16	0.23	2.0	44	1.70	0.27	1.5	47	1.45	0.21	1.0
(67 – 77]	43	2.84	0.30	3.0	42	2.17	0.32	2.0	48	1.65	0.27	1.0
> 77	40	2.70	0.33	2.0	48	1.60	0.21	1.5	48	2.06	0.27	2.0

Exacerbation Count at 1 Year vs. Burden of Disease

BL	**Placebo**				**Low Dose**				**High Dose**			
BOD	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< =771	48	1.40	0.18	1.0	51	1.0	0.16	1.0	42	0.74	0.14	0.5
(771-1991]	40	1.25	0.19	1.0	45	1.11	0.15	1.0	54	0.89	0.15	1.0
(1992-3972]	46	1.87	0.19	2.0	54	0.91	0.13	1.0	40	0.90	0.17	1.0
>3972	53	1.45	0.16	1.0	39	1.0	0.16	1.0	48	1.15	0.16	1.0

Exacerbation Count at 2 Years vs. Burden of Disease

BL	**Placebo**				**Low Dose**				**High Dose**			
BOD	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< = 771	48	2.42	0.29	2.0	51	1.76	0.28	2.0	42	1.69	0.29	1.0
(771-1991]	40	2.1	0.31	1.5	45	1.89	0.24	2.0	54	1.67	0.24	1.0
(1992-3972]	46	2.96	0.32	3.0	54	1.72	0.22	1.0	40	1.60	0.27	1.0
>3972	53	2.68	0.26	2.0	39	1.95	0.28	2.0	48	1.96	0.28	1.5

Exacerbation Count at 1 Year vs. Age

BL	**Placebo**				**Low Dose**				**High Dose**			
Age	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
<= 29.1	47	1.55	0.21	1.0	44	1.23	0.19	1.0	48	0.98	0.15	1.0
(29.1-34.9]	53	1.70	0.16	2.0	51	0.92	0.12	1.0	39	0.87	0.18	0.0
(34.9-40.4]	40	1.23	0.17	1.0	54	1.11	0.14	1.0	44	0.93	0.17	1.0
> 40.4	47	1.45	0.18	1.0	40	0.70	0.13	0.5	53	0.91	0.14	1.0

Exacerbation Count at 2 Years vs. Age

BL	**Placebo**				**Low Dose**				**High Dose**			
Age	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< = 29.1	47	2.72	0.34	2.0	44	2.27	0.31	2.0	48	1.98	0.28	1.5
(29.1-34.9]	53	2.79	0.23	3.0	51	1.67	0.19	2.0	39	1.53	0.29	1.0
(34.9-40.4]	40	2.25	0.28	2.0	54	1.96	0.26	2.0	44	1.64	0.27	1.0
> 40.4	47	2.38	0.33	2.0	40	1.33	0.21	1.0	53	1.74	0.24	2.0

Percent Change BOD (0-24 months) Vs. EDSS

BL	**Placebo**				**Low Dose**				**High Dose**			
EDSS	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
0 - 1.5	58	39.11	12.5	11.14	52	8.53	5.64	-0.88	52	-0.27	3.13	-2.27
2 – 2.5	49	18.1	4.0	16.1	46	54.4	37.8	8.6	46	-2.97	2.89	-3.44
3 – 3.5	40	15.4	4.0	11.2	41	-3.13	3.26	-6.1	44	1.09	4.13	-1.53
>=4	25	12.2	3.2	5.4	32	13.6	13.2	-2.3	29	0.68	4.64	-6.91
Overall	172	23.70	4.54	10.96	171	19.01	10.7	-1.2	171	-0.49	1.73	-3.82

Percent Change BOD (0-24 months) Vs. Sex

BL	**Placebo**				**Low Dose**				**High Dose**			
SEX	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
Male	41	50.92	16.7	17.4	55	35.9	31.5	-1.1	58	4.1	3.0	0.7
Female	131	15.18	2.54	10.0	116	11.0	5.1	-1.4	113	-2.8	2.1	-5.8

Percent Change BOD (0-24 months) Vs. Base Weight

BL	**Placebo**				**Low Dose**				**High Dose**			
Weight	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< = 59	51	15.2	4.6	10.4	46	13.9	9.6	-0.5	39	-6.5	2.6	-6.0
(59 – 67]	47	11.0	4.0	3.2	41	3.0	5.7	-5.2	43	2.6	3.4	-2.0
(67 – 77]	38	18.0	4.3	11.7	38	5.8	7.2	-2.0	44	-2.0	3.5	-5.2
> 77	36	58.5	18.6	30.8	46	49.3	37.7	5.3	45	3.2	3.9	0.0

Percent Change BOD (0-24 months) Vs. Burden of Disease

BL	**Placebo**				**Low Dose**				**High Dose**			
BOD	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< =771	46	42.6	15.5	13.0	49	50.3	36.6	-4.7	38	-6.4	2.5	-7.9
(771-1991]	36	24.0	6.0	10.4	42	15.0	5.4	5.2	52	2.0	4.2	-1.8
(1992-3972]	44	19.9	3.6	18.2	49	1.9	3.3	-2.7	35	2.1	2.4	0.7
>3972	46	8.2	2.7	7.6	31	2.1	3.7	0.0	46	-0.4	3.4	-2.9

Percent Change BOD (0-24 months) Vs. Age

BL	**Placebo**				**Low Dose**				**High Dose**			
Age	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
<= 29.1	45	18.3	5.3	6.8	37	19.2	6.4	5.0	43	2.8	4.8	-1.4
(29.1-34.9]	48	14.7	3.5	13.1	47	7.6	9.2	-3.3	35	1.7	4.3	-3.9
(34.9-40.4]	37	54.3	18.4	25.7	48	48.5	36.4	3.6	42	-0.6	2.8	-3.9
> 40.4	42	12.8	4.0	8.6	39	-3.8	4.1	-3.6	51	-4.7	2.0	-4.7

Mean Number of Active Lesions Per Scan vs. EDSS

BL	**Placebo**				**Low Dose**				**High Dose**			
EDSS	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
0 - 1.5	62	3.2	0.6	2.3	56	2.3	0.6	0.6	57	1.3	0.4	0.3
2 – 2.5	52	3.7	0.5	2.6	50	2.2	0.5	0.9	47	0.7	0.2	0.3
3 – 3.5	44	3.9	0.7	2.4	45	1.3	0.3	0.8	47	1.5	0.4	0.5
>=4	26	2.6	0.5	1.9	34	1.7	0.4	0.9	34	0.9	0.2	0.5
Overall	184	3.4	0.3	2.3	185	1.9	0.2	0.8	182	1.1	0.2	0.5

Mean Number of Active Lesion Per Scan vs. Sex

BL	**Placebo**				**Low Dose**				**High Dose**			
SEX	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
Male	45	4.3	0.8	2.3	61	1.4	0.3	0.8	61	1.3	0.3	0.8
Female	138	3.1	0.3	2.3	124	2.2	0.3	0.8	121	1.0	0.2	0.3

Mean Number of Active Lesion Per Scan vs. Base Weight

BL	**Placebo**				**Low Dose**				**High Dose**			
Weight	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< = 59	53	3.1	0.5	2.0	53	2.5	0.6	0.8	41	0.9	0.2	0.3
(59 – 67]	49	2.3	0.4	1.3	43	1.6	0.4	0.8	47	1.3	0.4	0.5
(67 – 77]	42	4.6	0.8	2.8	41	1.3	0.3	0.5	47	1.1	0.3	0.5
> 77	40	3.9	0.6	2.9	48	2.1	0.5	0.9	47	1.1	0.2	0.5

Mean Number of Active Lesion Per Scan vs. Burden of Disease

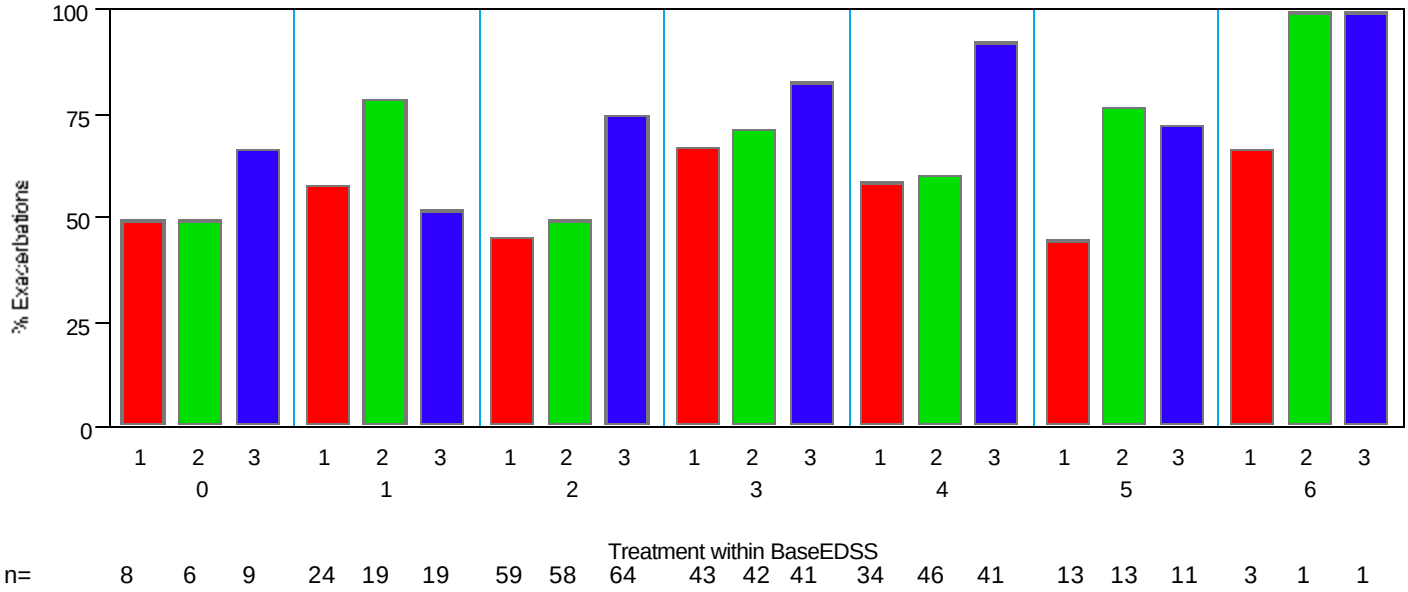
BL	**Placebo**				**Low Dose**				**High Dose**			
BOD	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
< =771	48	1.3	0.3	1.0	51	0.8	0.2	0.3	42	0.2	0.04	0.0
(771-1991]	40	2.6	0.3	2.1	45	1.9	0.5	1.0	53	0.9	0.19	0.5
(1992-3972]	45	4.2	0.5	3.0	52	1.9	0.3	1.0	39	1.4	0.40	0.7
>3972	51	5.2	0.8	3.3	37	3.6	0.8	1.8	48	2.0	0.43	1.0

Mean Number of Active Lesion Per Scan vs. Age

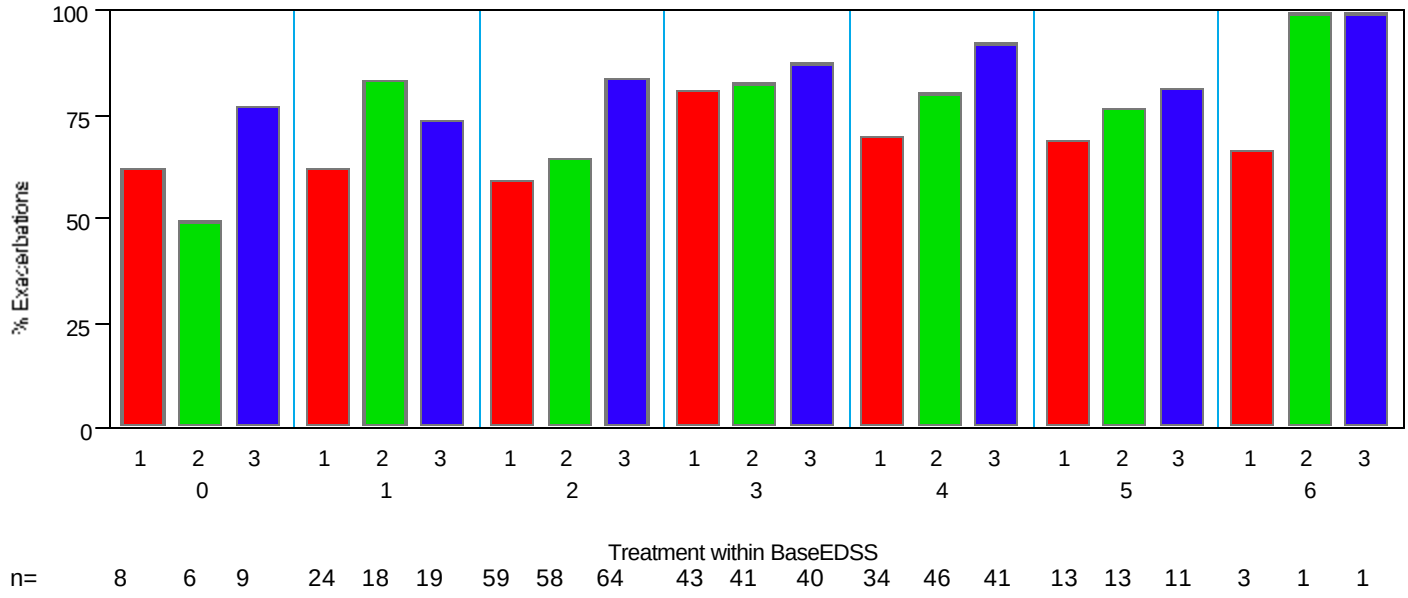
BL	**Placebo**				**Low Dose**				**High Dose**			
Age	n	mean	sem	median	n	mean	sem	median	n	mean	sem	median
<= 29.1	47	4.0	0.6	2.8	44	4.1	0.8	1.5	47	1.5	0.4	0.5
(29.1-34.9]	53	3.6	0.7	2.0	48	1.6	0.3	0.8	39	1.2	0.3	0.5
(34.9-40.4]	39	2.3	0.4	1.8	53	1.2	0.2	0.5	44	1.3	0.4	0.4
> 40.4	45	3.5	0.6	2.3	40	1.0	0.3	0.5	52	0.6	0.1	0.3

Appendix C

Histograms of Baseline EDSS Score and percent exacerbations for patients who had exacerbations at 1 Year (% in each category)



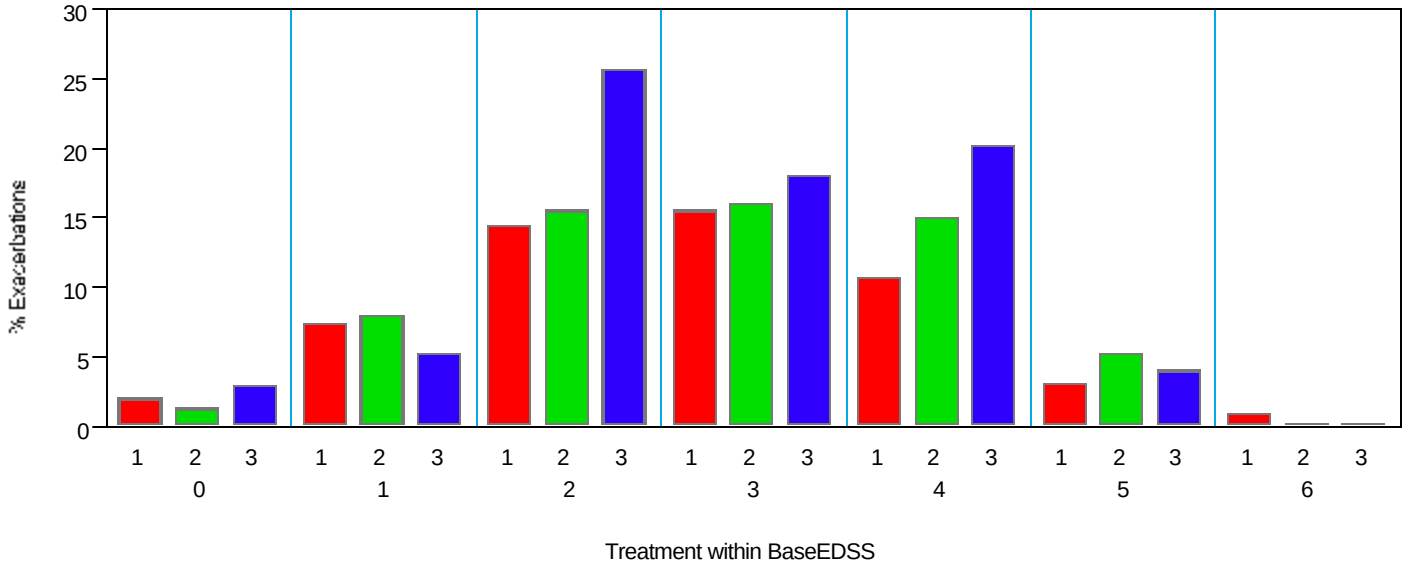
Histograms of Baseline EDSS Score and percent exacerbations for patients who had exacerbations at 2 Year (% in each category)



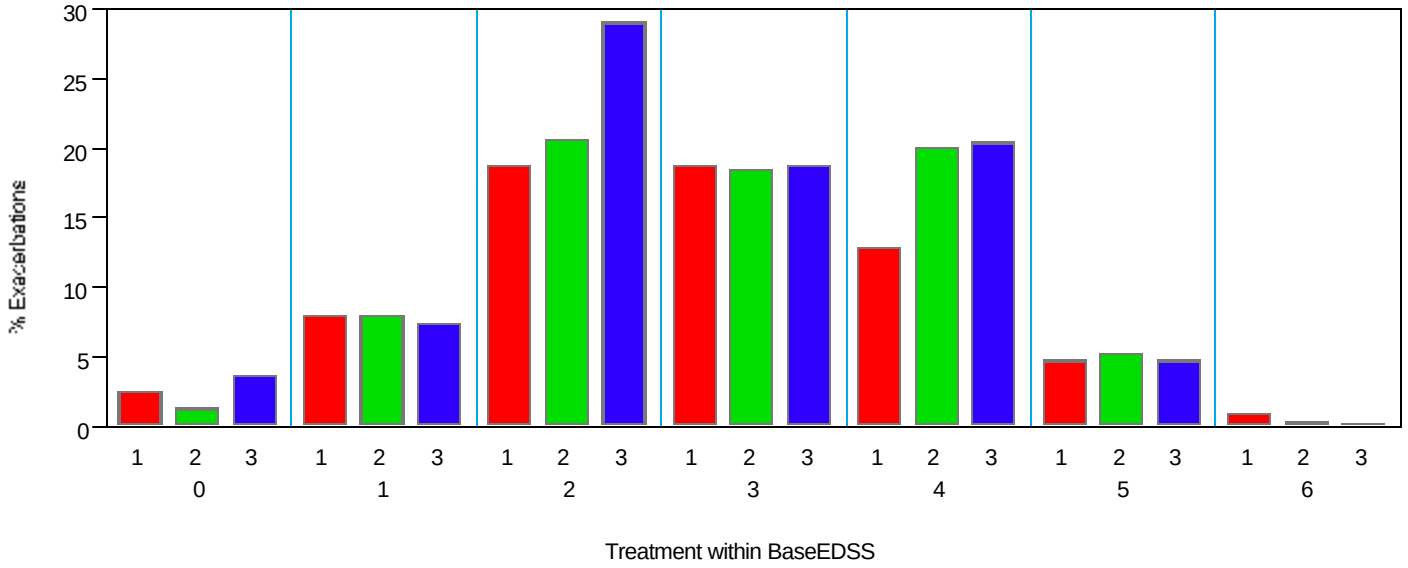
CODE Treatment	Dose	N at 1 Year	N at 2 Year
1	12MIU	184	184
2	6MIU	185	183
3	Placebo	186	185

EDSS Category	Baseline EDSS
0	0
1	0.5 or 1.0
2	1.5 or 2.0
3	2.5 or 3. 0
4	3.5 or 4. 0
5	4.5 or 5. 0
6	5.5 or 6. 0

Histograms of Baseline EDSS Score and percent exacerbations for patients who had exacerbations at 1 Year **(% of the total number of exacerbations)**



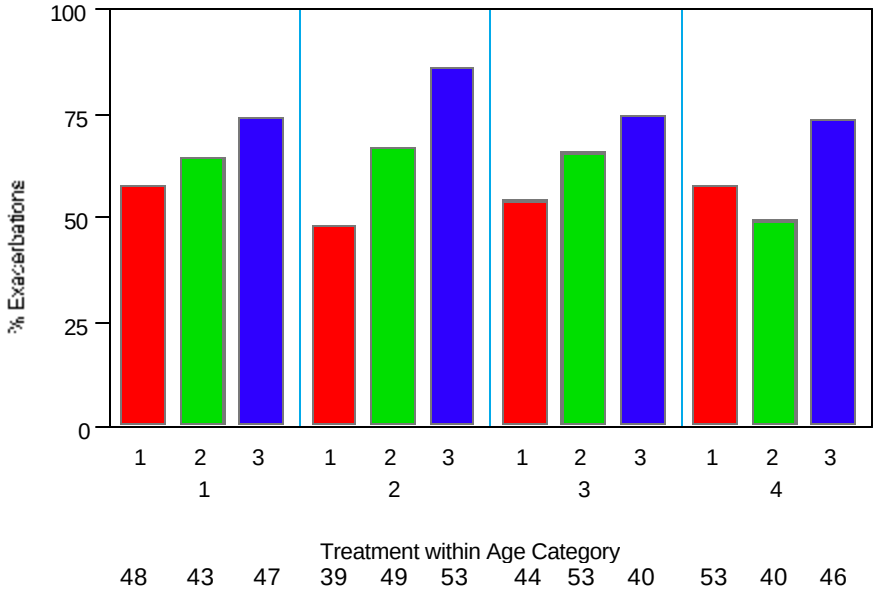
Histograms of Baseline EDSS Score and percent exacerbations for patients who had exacerbations at 2 Year Year **(% of the total number of exacerbations)**



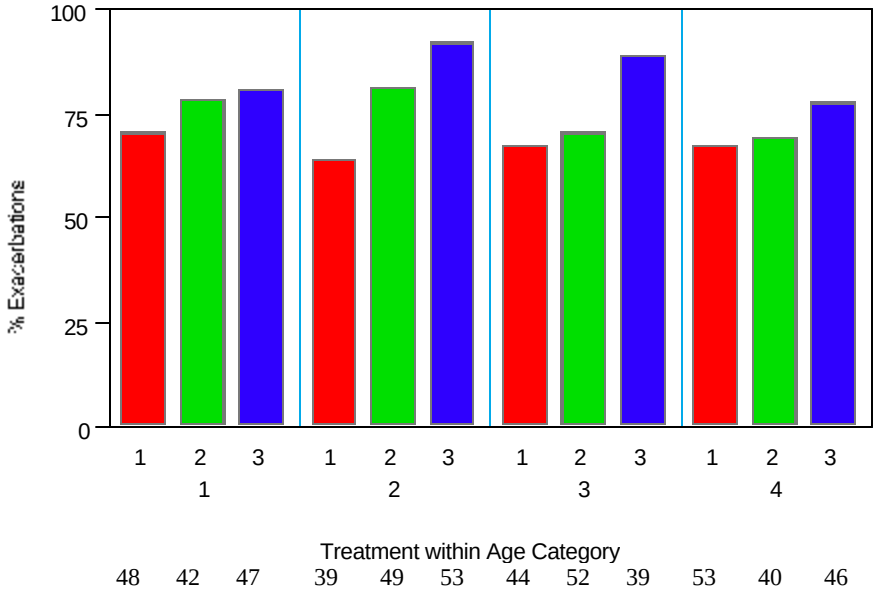
CODE

Treatment	Dose	N at 1 Year	N at 2 Year	EDSS Category	Baseline EDSS
1	12MIU	184	184	0	0
2	6MIU	185	183	1	0.5 or 1.0
3	Placebo	186	185	2	1.5 or 2.0
				3	2.5 or 3. 0
				4	3.5 or 4. 0
				6	4.5 or 5. 0
				6	5.5 or 6. 0

Histograms of Baseline Age Category and percent exacerbations for patients who had exacerbations at 1 Year **(% in each category)**



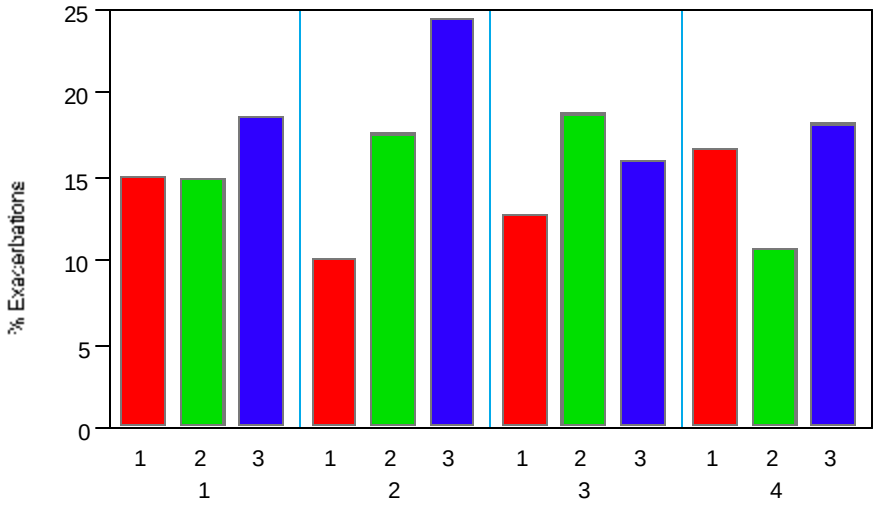
Histograms of Baseline Age Category and percent exacerbations for patients who had exacerbations at 2 Year **(% in each category)**



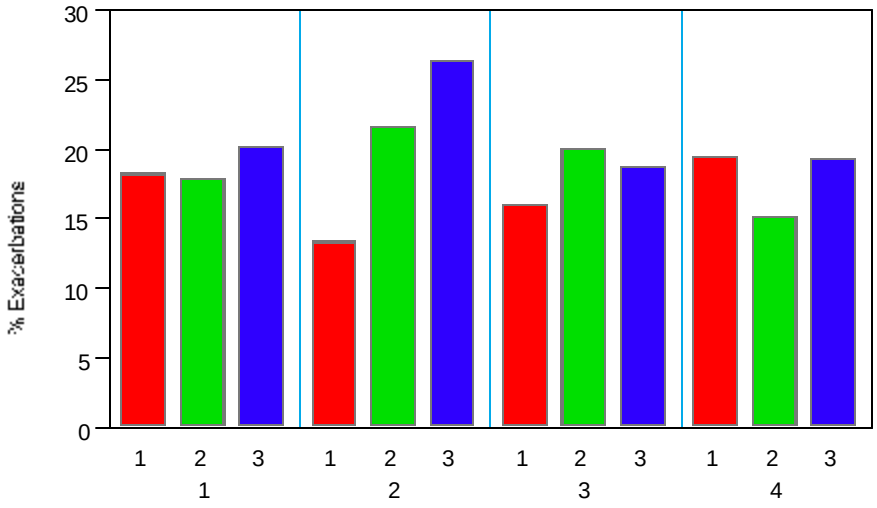
CODE

Treatment	Dose	N 1 Year	N 2Years	Age Category	Baseline Age
1	12MIU	184	184	1	< 29.1 years (25th percentile in combined)
2	6MIU	185	183	2	29.1 to 34.9 years (50th percentile)
3	Placebo	186	185	3	34.9 to 40.4 years (75th percentile)
				4	> 40.4 years

Histograms of Baseline Age Category and percent exacerbations for patients who had exacerbations at 1 Year **(% of the total number of exacerbations)**

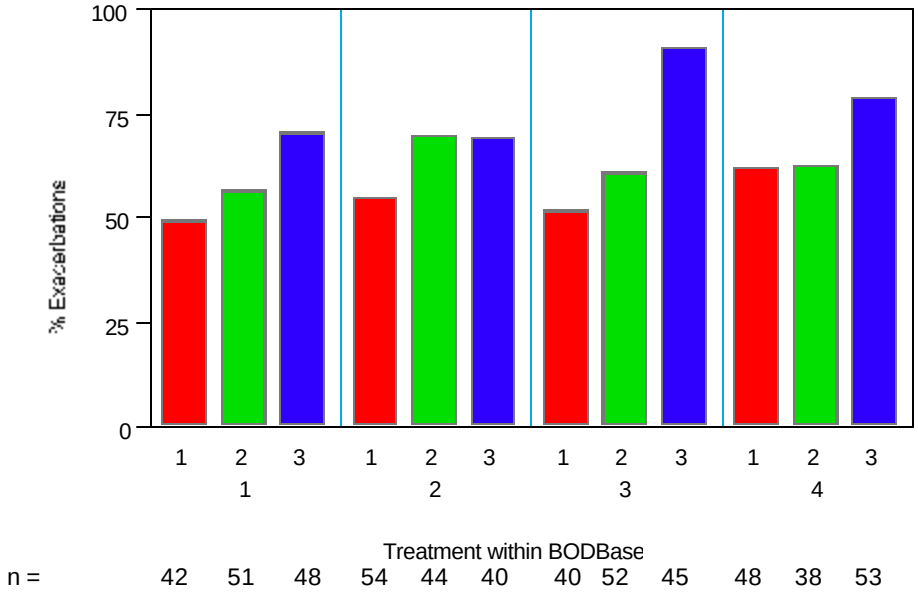


Histograms of Baseline Age Category and percent exacerbations for patients who had exacerbations at 2 Year **(% of the total number of exacerbations)**

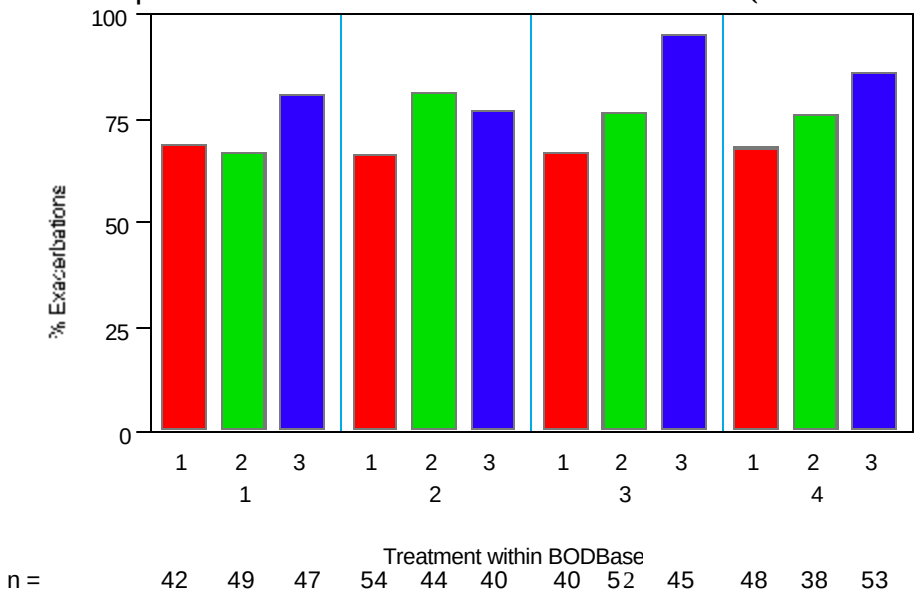


Treatment	CODE Dose	N 1 Year	N 2Years	Age Category	Baseline Age
1	12MIU	184	184	1	< 29.1 years (25th percentile in combined)
2	6MIU	185	183	2	29.1 to 34.9 years (50th percentile)
3	Placebo	186	185	3	34.9 to 40.4 years (75th percentile)
				4	> 40.4 years

Histograms of Baseline Burden of Disease (BOD) Category and percent exacerbations for patients who had exacerbations at 1 Year **(% in each category)**



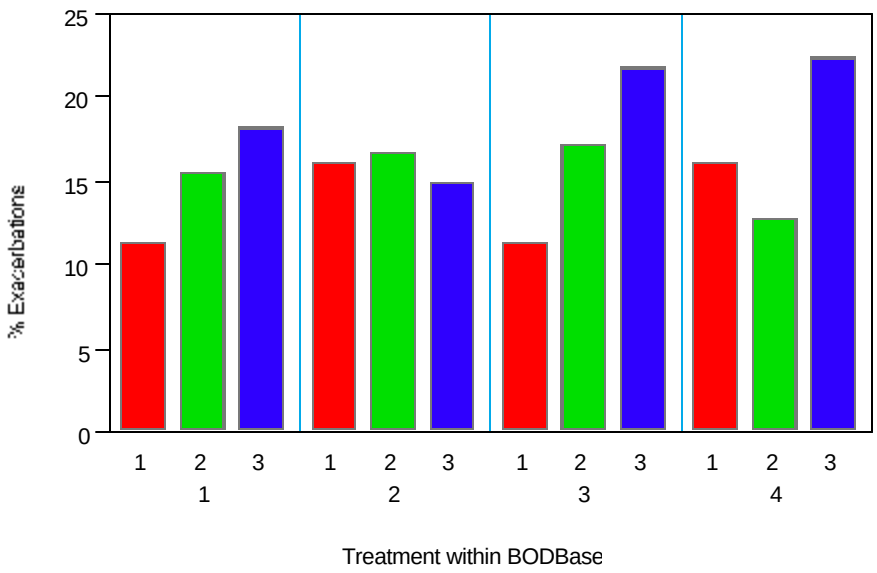
Histograms of Baseline Burden of Disease (BOD) Category and percent exacerbations for patients who had exacerbations at 2 Year **(% in each category)**



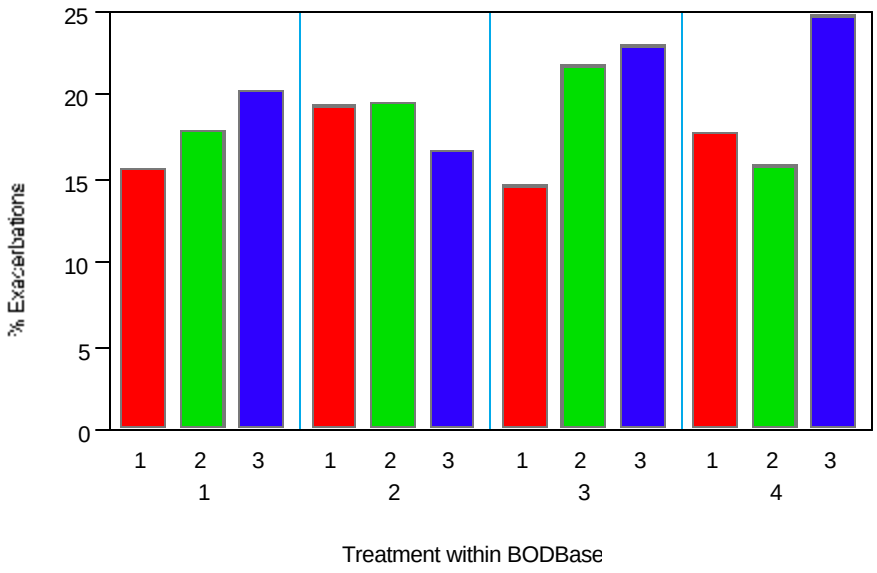
CODE

Treatment	Dose	N 1 Yr	N 2 Yr	BODCategory	Baseline Burden of Disease(BOD)
1	12MIU	184	184	1	< = 771 (25th percentile in combined data)
2	6MIU	185	183	2	771 to 1992 (50th percentile)
3	Placebo	186	185	3	1992 to 3972 (75th percentile)
				4	> 3973

Histograms of Baseline Burden of Disease (BOD) Category and percent exacerbations for patients who had exacerbations at 1 Year **(% of the total number of exacerbations)**

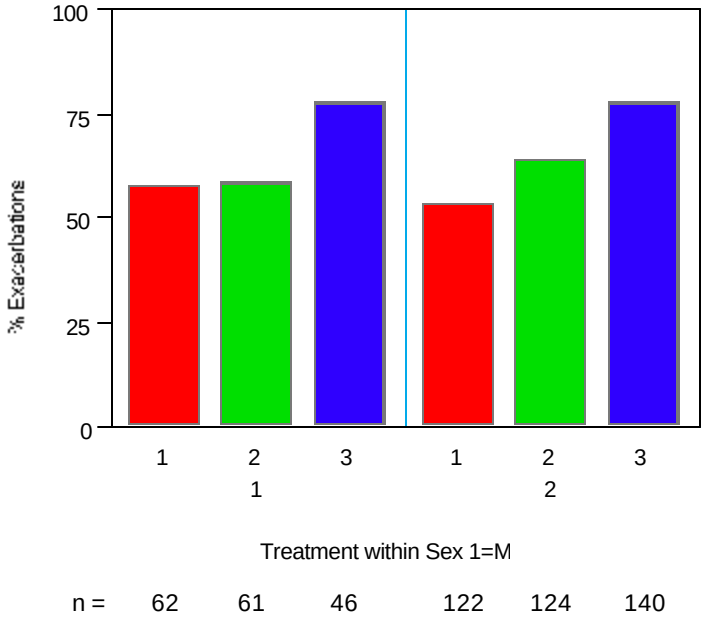


Histograms of Baseline Burden of Disease (BOD) Category and percent exacerbations for patients who had exacerbations at 2 Year **(% of the total number of exacerbations)**

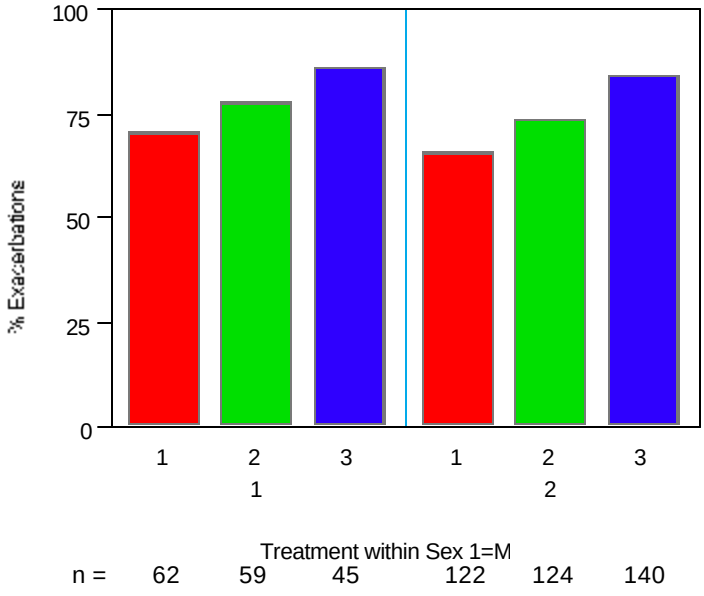


CODE Treatment	Dose	N 1 Yr	N 2 Yr	BODCategory	Baseline Burden of Disease(BOD)
1	12MIU	184	184	1	< = 771 (25th percentile in combined data)
2	6MIU	185	183	2	771 to 1992 (50th percentile)
3	Placebo	186	185	3	1992 to 3972 (75th percentile)
				4	> 3973

Histograms of Sex Category and percent exacerbations for Patients who had exacerbations at 1 Year **(% in each category)**



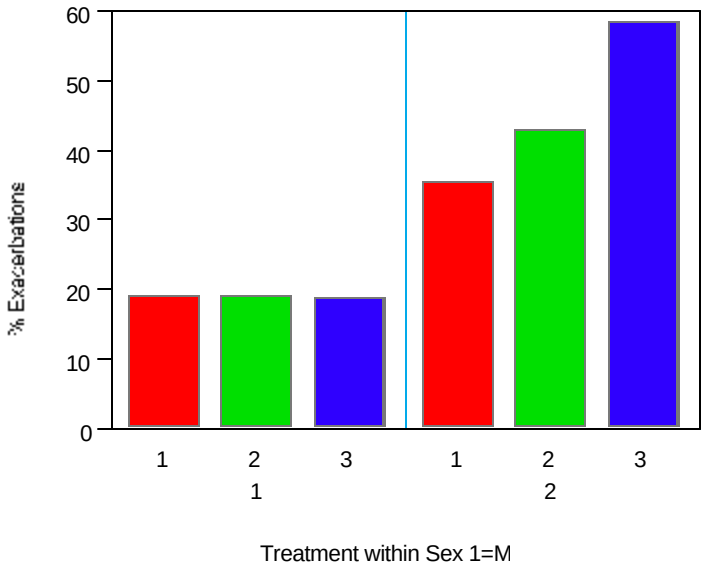
Histograms of Sex Category and percent exacerbations for Patients who had exacerbations at 2 Year **(% in each category)**



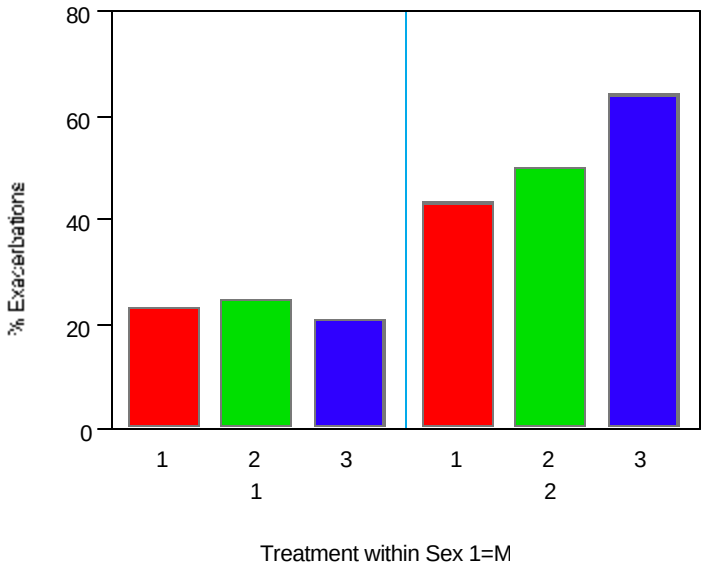
CODE

Treatment	Dose	N at 1 Year	N at 2 Year	Sex	Category
1	12MIU	184	184	1	Male
2	6MIU	185	183	2	Female
3	Placebo	186	185		

Histograms of Sex Category and percent exacerbations for patients
who had exacerbations at 1 Year **(% of the total number of exacerbations)**



Histograms of Sex Category and percent exacerbations for patients
who had exacerbations at 2 Year **(% of the total number of exacerbations)**



CODE

Treatment	Dose	N at 1 Year	N at 2 Year	Sex	Category
1	12MIU	184	184	1	Male
2	6MIU	185	183	2	Female
3	Placebo	186	185		

Appendix D

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis over all- all three groups (placebo, 6 & 12 MIU)

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT1 Exacerbation Free at 1 Yr (Y=0/N=1)
Response Levels: 2
Number of Observations: 555
Link Function: Logit

Response Profile

Ordered Value	B_COUNT1	Count
1	1	363
2	0	192

WARNING: 5 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	0.6369	0.0892	50.9410	0.0001	.	.

Residual Chi-Square = 29.1460 with 5 DF (p=0.0001)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	20.7629	0.0001	Treatment
EDSSCAT	5.1033	0.0239	Baseline EDSS Category
BODCAT	3.2849	0.0699	Burden of Disease Category
AGECAT	1.1071	0.2927	Age Category
SEX	0.2417	0.6230	Sex

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis over all- all three groups (placebo, 6 & 12 MIU)

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates for variables in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.8038	0.3061	6.8938	0.0086	.	.
TREAT	1	0.5132	0.1136	20.4099	0.0001	0.231235	1.671
EDSSCAT	1	0.1647	0.0722	5.2027	0.0226	0.115803	1.179

Residual Chi-Square = 3.4624 with 3 DF (p=0.3257)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	1.7788	0.1823	Burden of Disease Category
AGECAT	1.9078	0.1672	Age Category
SEX	0.0755	0.7835	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis over all- all three groups (placebo, 6 & 12 MIU)

The LOGISTIC Procedure

Summary of Stepwise Procedure

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	20.7629	.	0.0001
2	EDSSCAT		2	5.2484	.	0.0220

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing high dose (12 MIU) to placebo

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT1 Exacerbation Free at 1 Yr (Y=0/N=1)
Response Levels: 2
Number of Observations: 370
Link Function: Logit

Response Profile

Ordered Value	B_COUNT1	Count
1	1	247
2	0	123

WARNING: 1 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	0.6972	0.1104	39.9135	0.0001	.	.

Residual Chi-Square = 28.0666 with 5 DF (p=0.0001)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	21.1423	0.0001	Treatment
EDSSCAT	4.7615	0.0291	Baseline EDSS Category
BODCAT	3.6100	0.0574	Burden of Disease Category
AGECAT	0.1379	0.7103	Age Category
SEX	0.0006	0.9812	Sex

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing high dose (12 MIU) to placebo

Analysis of Maximum Likelihood Estimates for variables in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.8400	0.3416	6.0478	0.0139	.	.
TREAT	1	0.5294	0.1163	20.7054	0.0001	0.292258	1.698
EDSSCAT	1	0.2001	0.0899	4.9565	0.0260	0.142153	1.222

Residual Chi-Square = 2.3135 with 3 DF (p=0.5099)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	2.1257	0.1448	Burden of Disease Category
AGECAT	0.3135	0.5756	Age Category
SEX	0.1022	0.7492	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

Summary of Stepwise Procedure for variables in the model

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	21.1423	.	0.0001
2	EDSSCAT		2	5.0222	.	0.0250

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing low dose (6 MIU) to placebo

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT1 Exacerbation Free at 1 Yr (Y=0/N=1)
Response Levels: 2
Number of Observations: 371
Link Function: Logit

Response Profile

Ordered Value	B_COUNT1	Count
1	1	261
2	0	110

WARNING: 5 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	0.8640	0.1137	57.7733	0.0001	.	.

Residual Chi-Square = 21.1809 with 5 DF (p=0.0007)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	10.3469	0.0013	Treatment
EDSSCAT	5.4655	0.0194	Baseline EDSS Category
BODCAT	2.3959	0.1217	Burden of Disease Category
AGECAT	1.8548	0.1732	Age Category
SEX	0.6753	0.4112	Sex

The merged Database for exacerbations at the end of year 1
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing low dose (6 MIU) to placebo

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates for variables in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-1.3016	0.6859	3.6010	0.0577	.	.
TREAT	1	0.7973	0.2378	11.2358	0.0008	0.220073	2.219
EDSSCAT	1	0.2888	0.0988	8.5409	0.0035	0.199708	1.335
AGECAT	1	-0.2253	0.1116	4.0745	0.0435	-0.136116	0.798

Residual Chi-Square = 0.8186 with 2 DF (p=0.6641)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	0.4462	0.5041	Burden of Disease Category
SEX	0.3751	0.5402	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

Summary of Stepwise Procedure for variables in the model

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	10.3469	.	0.0013
2	EDSSCAT		2	6.4659	.	0.0110
3	AGECAT		3	4.1121	.	0.0426

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis over all- all three groups (placebo, 6 & 12 MIU)

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT2 Exacerbation Free (Y=0/N=1) at 2 Years
Response Levels: 2
Number of Observations: 552
Link Function: Logit

Response Profile

Ordered Value	B_COUNT2	Count
1	1	421
2	0	131

WARNING: 8 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	1.1674	0.1000	136.1696	0.0001	.	.

Residual Chi-Square = 24.6250 with 5 DF (p=0.0002)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	15.5603	0.0001	Treatment
EDSSCAT	5.7408	0.0166	Baseline EDSS Category
BODCAT	1.7340	0.1879	Burden of Disease Category
AGECAT	1.4593	0.2270	Age Category
SEX	0.2730	0.6013	Sex

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis over all- all three groups (placebo, 6 & 12 MIU)

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates for variables in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.2952	0.3315	0.7931	0.3732	.	.
TREAT	1	0.4977	0.1275	15.2347	0.0001	0.224540	1.645
EDSSCAT	1	0.1938	0.0808	5.7511	0.0165	0.136441	1.214

Residual Chi-Square = 3.3160 with 3 DF (p=0.3454)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	0.6257	0.4289	Burden of Disease Category
AGECAT	2.4905	0.1145	Age Category
SEX	0.4896	0.4841	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

Summary of Stepwise Procedure

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	15.5603	.	0.0001
2	EDSSCAT		2	5.8142	.	0.0159

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing high dose (12 MIU) to placebo

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT2 Exacerbation Free (Y=0/N=1) at 2 Years
Response Levels: 2
Number of Observations: 369
Link Function: Logit

Response Profile

Ordered Value	B_COUNT2	Count
1	1	283
2	0	86

WARNING: 2 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	1.1911	0.1231	93.5739	0.0001	.	.

Residual Chi-Square = 20.4997 with 5 DF (p=0.0010)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	15.7524	0.0001	Treatment
EDSSCAT	3.6043	0.0576	Baseline EDSS Category
BODCAT	0.9921	0.3192	Burden of Disease Category
AGECAT	0.3719	0.5420	Age Category
SEX	0.0647	0.7991	Sex

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing high dose (12 MIU) to placebo

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates for variables in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.2593	0.3661	0.5016	0.4788	.	.
TREAT	1	0.5128	0.1314	15.2334	0.0001	0.283117	1.670
EDSSCAT	1	0.1910	0.0993	3.7013	0.0544	0.135872	1.210

Residual Chi-Square = 1.0923 with 3 DF (p=0.7789)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	0.3054	0.5805	Burden of Disease Category
AGECAT	0.5841	0.4447	Age Category
SEX	0.3211	0.5709	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

Summary of Stepwise Procedure

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	15.7524	.	0.0001
2	EDSSCAT		2	3.7417	.	0.0531

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing low dose (6 MIU) to placebo

The LOGISTIC Procedure

Data Set: WORK.TEMP
Response Variable: B_COUNT2 Exacerbation Free (Y=0/N=1) at 2 Years
Response Levels: 2
Number of Observations: 368
Link Function: Logit

Response Profile

Ordered Value	B_COUNT2	Count
1	1	296
2	0	72

WARNING: 8 observation(s) were deleted due to missing values for the response or explanatory variables.

Stepwise Selection Procedure

Step 0. Intercept entered:

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	1.4137	0.1314	115.7409	0.0001	.	.

Residual Chi-Square = 15.2301 with 5 DF (p=0.0094)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
TREAT	5.8407	0.0157	Treatment
EDSSCAT	4.1465	0.0417	Baseline EDSS Category
BODCAT	2.9886	0.0839	Burden of Disease Category
AGECAT	1.7269	0.1888	Age Category
SEX	0.1547	0.6941	Sex

The merged Database for exacerbations at the end of year 2
Age Category, Sex, Burden of Disease and base EDSS category
Logistic Regression Analysis comparing low dose (6 MIU) to placebo

The LOGISTIC Procedure

Analysis of Maximum Likelihood Estimates in the model

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.4465	0.7829	0.3253	0.5684	.	.
TREAT	1	0.6969	0.2742	6.4594	0.0110	0.192381	2.008
EDSSCAT	1	0.2927	0.1138	6.6142	0.0101	0.202667	1.340
AGECAT	1	-0.2438	0.1284	3.6055	0.0576	-0.147465	0.784

Residual Chi-Square = 1.2569 with 2 DF (p=0.5334)

Analysis of Variables Not in the Model

Variable	Score Chi-Square	Pr > Chi-Square	Variable Label
BODCAT	0.9973	0.3180	Burden of Disease Category
SEX	0.2703	0.6031	Sex

NOTE: No (additional) variables met the 0.1 significance level for entry into the model.

Summary of Stepwise Procedure

Step	Variable Entered	Removed	Number In	Score Chi-Square	Wald Chi-Square	Pr > Chi-Square
1	TREAT		1	5.8407	.	0.0157
2	EDSSCAT		2	4.8089	.	0.0283
3	AGECAT		3	3.6460	.	0.0562